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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number: PCT/HU91/00006 (22) International Filing Date: 8 February 1991 (08.02.91) (30) Priority data: 808/90 15 February 1990 (15.02.90) HU (71) Applicant (for all designated States except US): CHINOIN GYÓGYSZER ÉS VEGYÉSZETI TERMÉKEK GYÁ- RA RT.[HU/HU]; Tó utca 1-5, H-Budapest IV (HU). (72) Inventor; and (75) Inventor/Applicant (for US only) : Z.SZABÓ, Anna [HU/ HU]; Farkashida 17, H-1163 Budapest (HU). (74) Agent: CHINOIN RT.; Division for Industrial Rights, Tó utca 1-5, H-1045 Budapest (HU).		(81) Designated States: AT (European patent), AU, BE (Euro- pean patent), CA, CH (European patent), DE (Euro- pean patent), DK (European patent), ES (European pa- tent), FI, FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, KR, LU (European patent), NL (European patent), NO, PL, SE (European patent), SU, US. Published <i>With international search report.</i>
(54) Title: EYE-DROP (57) Abstract The invention relates to an eye-drop, characterized by, that it contains, 0,02 - 0,1 mass % of primycin, 15,0 - 25,0 mass % of pyrrolidon-2, 12,0 - 25,0 mass % of polyoxyethylene-660-hydroxystearate, 1,0 - 5,0 mass % of polyvinyl-pyrrolidon and distilled water to complete to 100 mass percent.		

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EYE-DROP

The invention relates to a stable aqueous solution containing as active ingredient primycin and to a process for
5 the preparation thereof.

Subjects of the present invention are further therapeutical compositions prepared from the stable aqueous solution.

10

Primycin is a macrolide antibiotic agent, which is characterized in the literature (J. Chem. Soc. Perkin I. 1974, p. 816) by a single formula:

/5-(18-(α -D-arabinofuranosyloxy)-2-butyl-3,7,11,15,19,21,
15 23,25,27-nonahydroxy-4,16,32,34-tetramethyl-1-oxo-oxacyclohexatriakonta-16,32-diene-35-yl-)/4-hydroxyhexyl/guanidium-sulphate.

Although the above literature describes its structure by a single formula, it is known, that it is an antibiotic-mixture
20 consisting of several components (Hungarian Applications No. 2125/84 and 2869/84).

Primycin is a natural antibiotic agent originating from the fungal strain culture *Thermopolyspora galeriensis*, its
25 preparation via fermentation is described in the Hungarian Patent Specification No. 153.593. Primycin is an antibiotic agent of a large spectrum, and it is firstly effective against gram positive bacteria and against polyresistent humanpathogenic strains too.

30

Primycin can be effectively applied for the treatment of epithelium lesions, in the urology, surgery, gynecology, dermatology, in the case of household lesions and for the treatment of burns respectively.

35

In the course of its application neither resistance nor, allergic reactions were experienced.

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There are known further combinations of primycin with other antibiotics (Hungarian Patent Specification No. 158.241).

5 Although primycin is a very effective antibiotic, its
therapeutical utilization was made extraordinarily difficult
since it is practically insoluble in water.
Thus, several efforts had earlier been made to eliminate
these difficulties and to prepare pharmaceutical compositi-
10 ons containing primycin in a therapeutically well utilizable
form while maintaining its efficiency as a whole.

The Hungarian Patent Specification No. 173.708 publishes
heterocolloidal therapeutical compositions containing
15 primycin. Their disadvantage is the low primycin content
(0.2-1.0 %). Further the ethyl alcohol used for the
preparation of the heterocolloidal solution has in some cases
skin irritating effect and in the case the alcohol is
vaporized from the treated surface one part of the primycin
20 is running down from the skin without exerting a biological
effect. This formulation cannot be used to prepare eye-drops.

The Hungarian Patent Specification No. 194.493 describes
a basic gel containing primycin and N-methyl-pyrrolidon from
25 which therapeutical compositions and different gels were
prepared. This composition having a gel consistency is useful
to incorporate the active ingredient practically in all
galenic forms such as ointments, creams, foams and the like,
however it is not useful to prepare eye-drops.

30

The aim of our invention was to prepare a stable aqueous
solution containing primycin as active ingredient, which is
free from alcohol and does not contain eye-irritating sub-
stances and this way it is suitable for the preparation of
35 eye-drops.

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According to the facts set forth above the invention relates to eye-drops characterized by, that they contain

- 0,02 - 0,1 mass % of primycin,
- 15,0 - 25,0 mass % of pyrrolidon,
- 5 12,0 - 25,0 mass % of polyoxyethylene-660-hydroxystearate,
- 1,0 - 5,0 mass % of polyvinyl-pyrrolidon and
- distilled water needed to complete to 100 mass %.

The eye-drops according to the invention are prepared in
10 a way, that primycin is dissolved by heating in pyrrolidon-2
(Soluphor P) and to the warm solution the polyoxyethylene-
-660-hydroxystearate (Solutol HS 15) and polyvinyl-pyrrolidon
are added. The distilled water is added to the system while
stirring quickly and the solution is cooled to room-tempera-
15 ture while stirring.

The eye-drops according to our invention cause no eye-
irritation by a 14 days treatment as it has been proved by
animal experiments carried out on New Zealand rabbits.
20

The eye-drops according to the invention may contain
beside the primycin known antimicrobial active ingredients
as norfloxacin, pefloxacin, cyprofloxacin, ofloxacin too.

25 The compositions according to the invention are
illustrated by the following non limiting Example.

EXAMPLE

An eye-drop with the following composition is prepared

	Primycin	0,05 mass %
5	Soluphor P	20,0 mass %
	Soluptol HS	15,0 mass %
	Polyvinyl-pyrrolidon	3,0 mass %
	Distilled water ad.	100,0 mass %


What we claim is:

1. Eye-drop, characterized by, that it contains
0,02 - 0,1 mass % of primycin
5 15,0 - 25,0 mass % of pyrrolidon-2
12,0 - 25,0 mass % of polyoxyethylene-660-hydroxy-
stearate
1,0 - 5,0 mass % of polyvinyl-pyrrolidon
and distilled water to complete to 100 mass
10 percents.
2. Eye-drop according to claim 1, characterized by,
that it contains
0,05 mass % of primycin
15 20,0 mass % of pyrrolidon-2
15,0 mass % of polyoxyethylene-660-hydroxystearate
3,0 mass % of polyvinyl-pyrrolidon
and distilled water to complete to 100 mass
percents.
20

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INTERNATIONAL SEARCH REPORT

International Application No PCT/HU 91/00006

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC		
Int.Cl. ⁵ : A 61 K 31/71, 9/08, 47/32		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
Int.Cl. ⁵ : A 61 K 31/00, 9/00, 47/00		
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		
AT		
III. DOCUMENTS CONSIDERED TO BE RELEVANT ⁹		
Category ⁹	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
A	WO, A1, 85/05 621 (CHINOIN GYOGYSZER ES VEGYESZETI TERMEKEK GYARA RT) 19 December 1985 (19.12.85), see claims 50,57,60; example 37.	(1,2)
A	AT, B, 344 885 (CHINOIN GYOGYSZER ES VEGYESZETI TERMEKEK GYARA RT) 15 December 1977 (15.12.77), see claim 1; examples 7,13.	(1,2)
A	GB, A, 1 512 604 (CHINOIN GYOGYSZER ES VEGYESZETI TERMEKEK GYARA RT) 01 June 1978 (01.06.78), see claims 1,5; examples 11,12.	(1,2)
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A	DE, A1, 3 104 282 (CHINOIN GYOGYSZER ES VEGYESZETI TERMEKEK GYARA RT) 28 October 1982 (28.10.82), see example 6.	(1,2)
A	CH, A, 543 278 (BURTON PARSONS CHEMICALS, INC.) 14 December 1973 (14.12.73), see claims 1,10-12; column 8, lines 22-54.	(1,2)
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>¹⁰ Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"A" document member of the same patent family</p> </div> </div>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search		Date of Mailing of this International Search Report
03 April 1991 (03.04.91)		12 April 1991 (12.04.91)
International Searching Authority		Signature of Authorized Officer
AUSTRIAN PATENT OFFICE		

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
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A	GB, A, 1 340 518 (BURTON PARSONS CHEMICALS, INC.) 12 December 1973 (12.12.73), see example 1; page 4, lines 11-16, 69-105.	(1,2)
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Anhang zum internationalen Recherchenbericht über die internationale Patentanmeldung Nr.

In diesem Anhang sind die Mitglieder der Patentfamilien der im obengenannten internationalen Recherchenbericht angeführten Patentedokumente angegeben. Diese Angaben dienen nur zur Unterrichtung und erfolgen ohne Gewähr.

Annex to the International Search Report on International Patent Application No. PCT/HU 91/00006.

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Annexe au rapport de recherche internationale relatif à la demande de brevet international n°.

La présente annexe indique les membres de la famille de brevets relatifs aux documents de brevets cités dans le rapport de recherche internationale visé ci-dessus. Les renseignements fournis sont donnés à titre indicatif et n'engagent pas la responsabilité de l'Office autrichien des brevets.

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